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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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In the Matter of the Application of: Gefter et al.

Serial No.: 08/300,510

Filed: September 2, 1994

For: COMPOSITIONS AND METHODS FOR ADMINISTERING TO HUMANS, PEPTIDES CAPABLE OF DOWN REGULATING AN ANTIGEN SPECIFIC IMMUNE RESPONSE

Attorney Docket No: IMI-045

Group Art Unit: 1816

Examiner: Cunningham, T. M.

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APPEAL BRIEF

As set forth in the notice of appeal received by the Patent Office on June 12, 1997, Appellants hereby appeal the final decision of the Examiner rejecting the pending claims of the above-identified application. A Third Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 is being filed on even date herewith. Upon entry of the Third Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, the Board of Patent Appeals and Interferences is requested to consider the Appeal Brief

filed on December 12, 1997, in lieu of this Appeal Brief, and substitute the Appendix of Claims that accompanies the Third Amendment after Final, for the claims on Appeal.

A check in the amount of $155.00 for the Appeal Brief Fee as set forth in 37 C.F.R. §1.17(f) was sent on December 12, 1997. No other fees are believed to be due in connection with the filing of this Appeal Brief.

Appellants respectfully request that the Board of Patent Appeals and Interferences reverse the Examiner's rejection of all the claims.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Immulogic Pharmaceutical Corporation.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, Appellants' legal representative or the assignees which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 103-144 are pending in this application. Claims 106 and 133 have been amended as described in the Third Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116, which is being filed on even date herewith. The amendment and/or cancellation of these claims reduces the number of issues for appeal. Upon entry of the Third Amendment After Final, Appellants' request that the Appendix of Pending Claims filed with the Third Amendment After Final be substituted for the claims on appeal.

IV. STATUS OF THE AMENDMENTS

An Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 was filed on June 10, 1997 in response to the final office action dated December 10, 1996 and was not entered. A Notice of Appeal was filed separately on June 10, 1997 and received by the U.S. Patent Office on June 12, 1997.

A Second Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 was filed on December 12, 1997 in response to the final office action dated June 10, 1997 and was not entered.

A Third Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 is being filed on even date herewith in response to the Advisory Action dated March 5, 1998. At the time the Amendment was filed, claims 103-144 were pending in the application. In the Third Amendment and Response to Final Office Action Pursuant to 37 C.F.R. §1.116 submitted herewith, claims 106 and 133 have been amended. The amendment of claim 106 corrects improper dependency and the amendment of claim 133 obviates the rejection of claim 133 under 35 U.S.C. §112, second paragraph and claims 103-144 as they encompass the use of nonimmunogenic peptides under 35 U.S.C. §112, first paragraph. Accordingly, the amendment of claim 133 reduces the number of issues for appeal.

V. SUMMARY OF THE INVENTION

Appellants' invention pertains to methods for treating allergy in humans by administering at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response, e.g., a specific immune response to a Fel dI allergen, in the human. The methods for down regulation of an antigen specific response are described in the present application at least at page 7, lines 7-26. The therapeutic compositions used in the claimed methods include at least one peptide having a defined sequence of amino acid residues comprising at least one T cell epitope

recognized by a T cell receptor specific for the protein allergen, e.g., the Fel dI allergen. These defined amino acid sequences comprising at least one T cell epitope recognized by a T cell receptor specific for the protein allergen are described in the present application at least at page 8, lines 16-34, and at page 8, line 35 through page 9, line 15. In one embodiment, the peptide is reproducible, purified to at least about 90-97% purity and is not conjugated to any other molecule. Methods for synthesizing such peptides as well as peptides which are reproducible, purified to at least about 90-97% purity and not conjugated to any other molecule are described in the present application art least at page 14, lines 8-30, ant at page 15, lines 8-19.

In another embodiment, Appellants' invention pertains to methods for treating allergy in humans by administering at least one therapeutic composition, as described above, in a dosage range of about 20μg - 1.5mg per kg body weight of peptide per dosage unit. Such methods as well as methods for formulating appropriate dosage units are described in the present application at least at page 18, lines 23-32, and at page 18, lines 34-38.

Appellants' invention further pertains to methods for treating allergy in humans by administering at least one therapeutic composition, as described above, which includes at least one peptide having a mean T cell stimulation index of about 2.5 determined in an *in vitro* T cell proliferation assay. Such methods as well as methods for determining and testing the T cell stimulation index are taught in the present application at least at page 9, lines 27-36.

Appellants' invention still further pertains to methods for treating allergy in humans by administering at least one therapeutic composition, as described above, which includes at least one peptide containing at least about 20% of the T cell epitopes recognized by T cell receptor specific for the Fel dI protein allergen or capable of mimicking a T cell epitope recognized by a T cell receptor specific for the protein allergen. Such methods as well as methods for calculating the sufficient percentage T

cell epitopes of the protein antigen of interest to induce T cell nonresponsiveness are described in the present application at least at page 12, line 18 through page 19, line 7.

Appellants' invention yet further pertains to methods for treating allergy in humans by administering at least one therapeutic composition, as described above, which includes at least one peptide which is modified by at least one amino acid substitution, addition, or deletion. Such methods, as well as methods for modifying the structure of a peptide, are described in the present application at least at page 11, lines 7-21.

Appellants' invention furthermore pertains to methods for treating allergy in humans by administering at least one therapeutic composition as described herein and which (a) includes a pharmaceutically acceptable carrier with at least one excipient, (b) is soluble in an aqueous solution at a physiologically acceptable pH, (c) includes an acceptable route of administration, (d) is administered in non-immunogenic form, (e) is administered over an appropriate time period, (f) is administered at the appropriate dosage, and (g) is administered to cause improvement in the patient's condition. These methods of treatment are described in the present application at least at page 15, line 25 through page 16, line 21, and at page 17, line 35 through page 19, line 4.

VI. STATEMENT OF ISSUES PRESENTED FOR REVIEW

Appellants present the following issues for review:

I. Whether claim 133 is indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention as required under 35 U.S.C. § 112, second paragraph.

II. Whether claims 133 and 103-144 as they encompass the use of nonimmunogenic peptides contain subject matter which is not described in the specification in such a way to enable one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention as required under 35 U.S.C. § 112, first paragraph.

III. Whether the methods encompassed by claims 103-144 are unpatentable as being obvious in view of the teachings of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

VII. GROUPING OF CLAIMS

Claims 103-144 are Appellants' principal claims on appeal. Claim 103 is an independent claim drawn to a method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least one T cell epitope recognized by a T cell receptor specific for the protein allergen, said peptide being reproducible, being purified to at least about 90% purity and not being conjugated to any other molecule.

Claim 105 is an independent claim drawn to a method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least one T cell epitope recognized by a T cell receptor specific for the protein allergen and being present in a dosage range of about 20 μg - 1.5 mg per kg body weight of peptide per dosage unit, said peptide being reproducible and not being conjugated to any other molecule.

Claim 108 is an independent claim drawn to a method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least about 20% of the T cell epitopes recognized by T cell receptors specific for the protein allergen, said peptide being reproducible and not being conjugated to any other molecule.

Claim 110 is an independent claim drawn to a method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide being reproducible, being purified to at least about 90% purity and not being conjugated to any other molecule, said peptide being capable of mimicking a T cell epitope recognized by a T cell receptor specific for the protein allergen.

Claim 112 is an independent claim drawn to a method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide being reproducible and purified to at least about 90% purity, said peptide being derived from an antigen which is a bystander antigen to the protein allergen to which a human is sensitive.

Claims 104, 106, 109, 111, 113-144 depend from the above described independent claims.

Claims 104, 106, 109, 111, and 113 which depend from claims 103, 105, 108, 110, and 112, respectively, are directed to a peptide comprising 50 amino acid residues or less.

Claim 107, which depends from claim 105, is directed to a peptide having a mean T cell stimulation index of at least about 2.5 determined in an *in vitro* T cell proliferation assay with T cells obtained from a population of at least 30 humans sensitive to the protein allergen.

Claim 114, which depends from any one of claims 103-113, is directed to a peptide modified by at least one amino acid substitution, addition or deletion, said peptide comprising a T cell epitope recognized by a T cell receptor specific for the protein allergen.

Claim 115, which depends from any one of claims 105-109, is directed to a peptide purified to at least about 90% purity. Claim 116, which depends from claim 115, is directed to a peptide purified to at least about 95% purity. Claim 117, which depends from claim 116, is directed to a peptide purified to at least about 97% purity.

Claim 118, which depends from any one of claims 103-104 and 110-113, is directed to a peptide purified to at least about 95% purity. Claim 119, which depends from claim 118, is directed to a peptide purified to at least about 97% purity.

Claims 120-122 depend from any one of claims 103-113. Claim 120 is directed to a peptide at least about 12 amino acid residues in length. Claim 121 is directed to at least one peptide comprising at least two peptides. Claim 122 is directed to a protein allergen selected from the group consisting of: a protein allergen of the genus *Dermatophagoides*; a protein allergen of the genus *Felis*; a protein allergen of the genus *Ambrosia*; a protein allergen of the genus *Lolium*; a protein allergen of the genus *Cryptomeria*; a protein allergen of the genus *Alternaria*; a protein allergen of the genus *Alder*; a protein allergen of the genus *Betula*; a protein allergen of the genus *Quercus*; a protein allergen of the genus *Olea*; a protein allergen of the genus *Artemisia*; a protein allergen of the genus *Plantago*; a protein allergen of the genus *Parietaria*; a protein allergen of the genus *Canine*; a protein allergen of the genus *Blattella*; a protein allergen of the genus *Apis*; a protein allergen of the genus *Cupressus*; a protein allergen of the genus *Juniperus*; a

protein allergen of the genus *Thuya*; a protein allergen of the genus *Chamaecyparis*; a protein allergen of the genus *Periplaneta*; a protein allergen of the genus *Agropyron*; a protein allergen of the genus *Secale*; a protein allergen of the genus *Triticum*; a protein allergen of the genus *Dactylis*; a protein allergen of the genus *Festuca*; a protein allergen of the genus *Poa*; a protein allergen of the genus *Avena*; a protein allergen of the genus *Holcus*; a protein allergen of the genus *Anthoxanthum*; a protein allergen of the genus *Arrhenatherum*; a protein allergen of the genus *Agrostis*; a protein allergen of the genus *Phleum*; a protein allergen of the genus *Phalaris*; a protein allergen of the genus *Paspalum*; and a protein allergen of the genus *Sorghum*.

Claim 123, which depends from claim 122, is directed to the protein allergen selected from the group consisting of: *Der p* I; *Der p* II; *Der p* III; *Der p* VII; *Der f* I; *Der f* II; *Der f* III; *Der f* VII; *Fel d* I; *Amb a* I.1; *Amb a* I.2; *Amb a* I.3; *Amb a* I.4; *Amb a* I; *Lol p* I; *Lol p* II; *Lol p* III; *Lol p* IV; *Lol p IX* (*Lol p* V or *Lol p* Ib); *Cry j* I; *Cry j* II; *Can f* I; *Can f* II; *Jun s* I; *Jun v* I; *Dac g* I; *Poa p* I; *Phl p* I; and *Sor h* I.

Claim 124, which depends from claim 107, is directed to a peptide having a mean T cell stimulation index of at least about 3.0.

Claim 125, which depends from claim 124, is directed to a peptide having a mean T cell stimulation index of at least about 4.0.

Claim 126, which depends from claim 107, is directed to a peptide having a positivity index of at least 150.

Claim 127, which depends from claim 105, is directed to a peptide present in a dosage range of about 50 μg - 750 μg per kg body weight of peptide per dosage unit.

Claim 128, which depends from any one of claims 103-113, is directed to a composition further comprising a pharmaceutically acceptable carrier.

Claim 129, which depends from claim 128, is directed to a pharmaceutically acceptable carrier comprising at least one excipient selected from the group consisting of sterile water, sodium phosphate, mannitol, sorbitol, sodium chloride, and any combination thereof.

Claim 130, which depends from any one of claims 103-113, is directed to a composition soluble in an aqueous solution at a physiologically acceptable pH.

Claim 131, which depends from any one of claims 103-113, is directed to routes of administration selected from the group consisting of oral, intravenous, sublingual, transdermal, inhalation, subcutaneous and rectal.

Claim 132, which depends from claim 131, is directed to subcutaneous administration of said composition.

Claims 133-134 depend from any one of claims 103-113. Claim 133 is directed to administration in non-immunogenic form. Claim 134 is directed to administering an initial treatment of three to six dosages of said composition over a period of no more than 6 weeks.

Claim 135, which depends from claim 134, is directed to administering an additional administration of said composition at intervals of between about three months and one year after said initial treatment.

Claims 136-138 depend from any one of claims 103-113. Claim 136 is directed to initial treatment comprising increasing the dosage with each subsequent additional dosage of said composition. Claim 137 is directed to initial treatment comprising decreasing the dosage with each subsequent additional dosage of said composition. Claim 138 is directed to treatment resulting in a statistically significant improvement in symptoms caused by the human's immune response to the protein allergen.

Claims 139-141 depend from claim 128. Claim 139 is directed to treatment resulting in at least about 17.5% improvement, as compared to placebo, in symptoms caused by the human's immune response to the protein allergen. Claim 140 is directed to treatment resulting in at least about 9% improvement, as compared to placebo, in nasal symptoms caused by the human's immune response to the protein allergen. Claim 141 is directed to treatment resulting in at least about 17.5% improvement, as compared to placebo, in lung symptoms caused by the human's immune response to the protein allergen.

Claims 142-144 depend from claim 139. Claim 142 is directed to treatment resulting in at least about 23% improvement. Claim 143 is directed to treatment resulting in at least about 31% improvement. Claim 144 is directed to treatment resulting in at least about 28.5 % improvement.

The rejected claims do not stand or fall together for the reasons set forth below.

VIII. ARGUMENTS

Rejection of Claim 133 Under 35 U.S.C. § 112, second paragraph

Claim 133 was rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention. Specifically, the Examiner states that "[i]n claim 133 it is unclear what the metes and bounds of the term 'nonimmunogenic' are."

Appellants respectfully submit that the phrase "nonimmunogenic form" is described in the subject specification and is art recognized terminology. Claim 133 requires administration of peptides in "non-immunogenic ***form***." The meaning of the term "in non-immunogenic ***form***" is not only described in clear detail in Applicants' disclosure, but was also art-recognized at the time of the invention and therefore would have been clear to one of ordinary skill in the art. Evidence of such can be found in numerous references published prior to the filing date of the present application, such as

Kearney et al. (1994) *Immunity* 1:327-339, and Briner et al. (1993) *PNAS* 90: 7608-7613 discussed below.

As disclosed at page 7, lines 7-18, of the specification, stimulation of T cells requires two signals. The first signal is recognition of antigen presenting cells (APCs) by the T-cell receptor (TCR). The second signal is costimulation of T cells by a costimulatory or "second" signal produced by APCs in response to certain auxiliary stimuli, such as adjuvant. Without the occurrence of both T cell epitope recognition and costimulation by APCs, T cells are not stimulated and the various immune responses which normally ensue are not induced. This is believed to be due to the fact that, in the absence of an agent such as adjuvant which causes APCs to produce the second signal or costimulatory signal, competent APC's are not engaged in the stimulation of appropriate T cells. This can then result in T cell non-responsiveness or reduced T cell responsiveness.

Thus, Appellants disclosure makes it clear that the term "in non-immunogenic form" means in a form which does not include an agent, such as an adjuvant, which induces the co-stimulatory properties of APCs (see, e.g., page 6, line 27 and page 7, line 15 of the specification).

The meaning of the term "in non-immunogenic form" was also discussed extensively in the literature at the time the present application was filed. For example, Kearney et al. (1994) *Immunity* 1: 327-339 teach that "monomeric antigen ***is only immunogenic if injected locally in an adjuvant***" (see page 327) (emphasis added) based on the need for co-stimulation of T cells by APCs. The authors teach that adjuvant "induces local inflammation which enhances the adhesive and costimulatory properties of APC's" (see page 327).

The meaning of administration "in non-immunogenic form" is similarly discussed by Briner et al. (1993) *PNAS* 90: 7608-7613. Specifically, the authors state that "*in-vivo* tolerance to antigen challenge has been shown using . . . peptides administered in such a

way as to preclude the second signal [i.e., co-stimulation by APCs]" (see page 7608). Thus, the art came to know this mode of administration as administration ***in non-immunogenic form***.

Overall, both Appellants' disclosure and the literature at the time of the present invention would have made the metes and bounds of the term "in non-immunogenic form" clear to one of ordinary skill in the art. Accordingly, claim 133 is definite as required under 35 U.S.C. §112, second paragraph.

Rejection of Claims 133 and 103-144 Under 35 U.S.C. § 112, first paragraph

Claims 133 and 103-144 as they encompass the use of nonimmunogenic peptides were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner states that "[t]he peptides in the claimed methods are 'immunogenic' as they induce immune responses in human patients, see e.g. page 23, line 26 of the specification."

As described above, Appellants submit that the phrase "in non-immunogenic form" is art-recognized and an example of a "non-immunogenic" form described in the present specification is a form "not containing adjuvant" (see e.g., page 6, line 27, and page 7, line 15 of the specification). Thus, Appellants assert that claim 133 and 103-144 contain subject matter which is described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

In addition, the statement by the Examiner that "***the peptides used in the claimed methods are immunogenic as they induce immune responses in human patients***" (emphasis added) is not entirely correct. T cell epitope containing peptides encompassed by the present claims are ***not*** immunogenic (as defined by T cell stimulation and the occurrence of various ensuing immune reactions such as recruitment of other immune cells, immunglobulins etc.) unless an agent - most commonly adjuvant - is administered

along with the peptides to induce the co-stimulatory action of APCs required to cause T cell stimulation.

Therefore, based on the above-described teachings of Appellants that T cell epitope containing peptides can be administered in non-immunogenic form ***simply by not including an agent which induces the co-stimulatory action of APCs***, Appellants respectfully submit that the subject matter of claims 133 and 103-144 are fully enabled. Indeed, Appellants' disclosure teaches the most common manner of administering peptides in non-immunogenic, namely by simply omitting any adjuvant (see e.g., page 6, line 27, and page 7, line 15 of the specification). Thus, the disclosure would have fully enabled one of ordinary skill in the art to have made and used (e.g., administered) the peptides encompassed by claims 133 and 1-3-144 without undue experimentation.

Appellants accordingly respectfully request that the rejection be withdrawn.

Rejection of Claims 103-144 Under 35 U.S.C. § 103 as Being Obvious in Light of Sehon et al., *J. Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991)

The present claims are drawn to a method of treating allergy in humans comprising administration of therapeutic compositions comprising one or more purified (e.g., to at least about 90% purity) T cell epitope containing peptides which have defined amino acid sequences and which are not conjugated to any other molecule. Thus, the compositions encompassed by the present claims provide the distinct advantage of being highly pure and reproducible, making them safer and eminently more suitable for human administration than compositions containing whole or partially digested native allergens obtained from crude allergen extracts.

Sehon et al. teach that conjugation of PEG to peptides can render peptides nonimmunogenic or "tolerogenic." For example, Sehon et al, teach "that the PEG

conjugates did not induce anaphylatic death of animals and . . . therefore . . . appear to have the desirable properties of safe immunotherapeutic agents." Thus, the teachings of Sehon et al. would ***not*** have suggested the use of ***unconjugated*** peptides in therapeutic compositions, as claimed by Appellants. In fact, the authors teach directly ***away*** from the use of unconjugated peptides in compositions for human therapy, since they disclose that modification, such as PEG conjugation, is necessary to render the peptides tolerogenic and safe. Moreover, as previously pointed out by Appellants, the Examiner agreed during the personal interview that Sehon et al. ***does not teach or suggest the use of a peptide per se or a therapeutic composition containing a peptide.***

Michael et al. also fail to provide any teaching or suggestion which would have led one of ordinary skill in the art to the claimed invention. Michael et al. teach proteolytic digestion of primary pollen allergens to produce pollen specific polypeptides. Proteolytic digestion of native allergen generates an ***irreproducible*** milieu of polypeptide fragments which have an ***unknown variable composition*** following each digestion. Moreover, not all of the proteolytically digested peptides are certain to contain a T cell epitope. Nor are the peptides highly pure since they are present along with a variety of other contaminating proteins with which the allergen naturally occurs.

In contrast, Appellants claim therapeutic compositions made up of a ***reproducible*** selection of peptides all of which comprise at least one ***T cell epitope*** and which are ***purified to at least about 90%***. Accordingly, based on the teachings of Michael et al., the subject matter presently claimed by Appellants would not have been obvious to one of ordinary skill in the art. Indeed, Micheal et al. fail to provide any motivation at all to have made or used ***highly pure***, ***reproducible*** compositions of T cell epitope containing peptides in human immunotherapy, since they teach that compositions containing proteolytically cleaved allergens, which were known to be easier and less expensive to make, were sufficient for therapy.

Similar to Michael et al., Litwin et al. teach the use of compositions containing native peptic fragments obtained by digestion of chromatographic fractions enriched for ragweed allergen *Amb a* I. Thus, like Micheal et al., Litwin et al. fail to teach or suggest a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides which are ***purified to at least about 90%*** as claimed by Appellants.

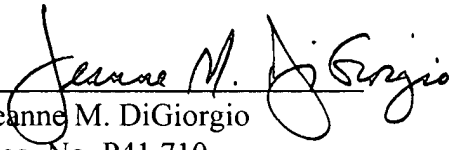
Kuo also fails to make up for the many aforementioned deficiencies in the teachings of the above-discussed references. Kuo merely teaches whole *Fel d* I protein modified by treatment with mild base or alkali conditions to reduce IgE reactivity. As previously acknowledged by the Examiner during the personal interview conducted on December 12, 1995, Kuo et al. do not teach or suggest peptides or compositions containing peptides useful for human administration, let alone ***highly pure, reproducible T cell epitope containing peptide compositions***.

In sum, none of the cited references, either alone or in combination, provide any teaching or suggestion which would have motivated one of ordinary skill in the art to make and use a therapeutic composition made up of a ***reproducible*** selection of ***T cell epitope*** containing peptides of which are ***purified to at least about 90%,*** as claimed by Appellants. Therefore, Appellants respectfully submit that claims 103-144 are patentable over Sehon et al., J. *Allergy Clin. Immunol.* 64:242-250 (1979), Michael et al., U.S. patent 4,338,297 (issued 1982) or Litwin et al., *Clin. Exp. Allergy* 21:457-465 (1991) or Kuo et al., U.S. patent 5,328,991 (filed 1991).

IV. CONCLUSION

Appellant submits that the pending claims are patentable and it is respectfully requested that the Board reverse the final rejection of all the claims for the reasons given above.

Respectfully submitted



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APPENDIX OF PENDING CLAIMS

103. A method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least one T cell epitope recognized by a T cell receptor specific for the protein allergen, said peptide being reproducible, being purified to at least about 90% purity and not being conjugated to any other molecule.

104. The method of claim 103, wherein the peptide comprises 50 amino acid residues or less.

105. A method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least one T cell epitope recognized by a T cell receptor specific for the protein allergen and being present in a dosage range of about 20 μg - 1.5 mg per kg body weight of peptide per dosage unit, said peptide being reproducible and not being conjugated to any other molecule.

106. The method of claim 104, wherein the peptide comprises 50 amino acid residues or less.

107. The method of claim 105, wherein the peptide has a mean T cell stimulation index of at least about 2.5 determined in an *in vitro* T cell proliferation assay with T cells obtained from a population of at least 30 humans sensitive to the protein allergen.

108. A method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide comprising at least about 20% of the T cell epitopes recognized by

T cell receptors specific for the protein allergen, said peptide being reproducible and not being conjugated to any other molecule.

109. The method of claim 108, wherein the peptide comprises 50 amino acid residues or less.

110. A method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide being reproducible, being purified to at least about 90% purity and not being conjugated to any other molecule, said peptide being capable of mimicking a T cell epitope recognized by a T cell receptor specific for the protein allergen.

111. The method of claim 110, wherein the peptide comprises 50 amino acid residues or less.

112. A method of treating allergy in humans comprising administering to a human at least one therapeutic composition in an amount sufficient to down regulate a protein allergen specific immune response in the human, wherein the therapeutic composition comprises at least one peptide having a defined sequence of amino acid residues, said peptide being reproducible and purified to at least about 90% purity, said peptide being derived from an antigen which is a bystander antigen to the protein allergen to which a human is sensitive.

113. The method of claim 112, wherein the peptide comprises 50 amino acid residues or less.

114. The method as in any one of claims 103-113 wherein the peptide is modified by at least one amino acid substitution, addition or deletion, said peptide comprising a T cell epitope recognized by a T cell receptor specific for the protein allergen.

115. The method as in any one of claims 105-109, wherein the peptide is purified to at least about 90% purity.

116. The method of claim 115, wherein the peptide is purified to at least about 95% purity.

117. The method of claim 116, wherein the peptide is purified to at least about 97% purity.

118. The method as in any one of claims 103-104 and 110-113 wherein the peptide is purified to at least about 95% purity.

119. The method of claim 118, wherein the peptide is purified to at least about 97% purity.

120. The method as in any one of claims 103-113, wherein the peptide is at least about 12 amino acid residues in length.

121. The method as in any one of claims 103-113, wherein the at least one peptide comprises at least two peptides.

122. The method as any one of claims 103-113, wherein the protein allergen is selected from the group consisting of: a protein allergen of the genus *Dermatophagoides*; a protein allergen of the genus *Felis*; a protein allergen of the genus *Ambrosia*; a protein allergen of the genus *Lolium*; a protein allergen of the genus *Cryptomeria*; a protein allergen of the genus *Alternaria*; a protein allergen of the genus *Alder*; a protein allergen of the genus *Betula*; a protein allergen of the genus *Quercus*; a protein allergen of the genus *Olea*; a protein allergen of the genus *Artemisia*; a protein allergen of the genus *Plantago*; a protein allergen of the genus *Parietaria*; a protein allergen of the genus *Canine*; a protein allergen of the genus *Blattella*; a protein allergen of the genus *Apis*; a protein allergen of the genus *Cupressus*; a protein allergen of the genus *Juniperus*; a protein allergen of the genus *Thuya*; a protein allergen of the genus *Chamaecyparis*; a protein allergen of the genus *Periplaneta*; a protein allergen of the genus *Agropyron*; a protein allergen of the genus *Secale*; a protein allergen of the genus *Triticum*; a protein allergen of the genus *Dactylis*; a protein allergen of the genus *Festuca*; a protein allergen of the genus *Poa*; a protein allergen of the genus *Avena*; a protein allergen of the genus *Holcus*; a protein allergen of the genus *Anthoxanthum*; a protein allergen of the genus *Arrhenatherum*; a protein allergen of the genus *Agrostis*; a protein allergen of the genus *Phleum*; a protein allergen of the genus *Phalaris*; a protein allergen of the genus *Paspalum*; and a protein allergen of the genus *Sorghum*.

123. The method of claim 122, wherein the protein allergen is selected from the group consisting of: *Der p* I; *Der p* II; *Der p* III; *Der p* VII; *Der f* I; *Der f* II; *Der f* III; *Der f* VII; *Fel d* I; *Amb a* I.1; *Amb a* I.2; *Amb a* I.3; *Amb a* I.4; *Amb a* II; *Lol p* I; *Lol p* II; *Lol p* III; *Lol p* IV; *Lol p IX* (*Lol p* V or *Lol p* Ib); *Cry j* I; *Cry j* II; *Can f* I; *Can f* II; *Jun s* I; *Jun v* I; *Dac g* I; *Poa p* I; *Phl p* I; and *Sor h* I.

124. The method of claim 107, wherein the peptide has a mean T cell stimulation index of at least about 3.0.

125. The method of claim 124, wherein the peptide has a mean T cell stimulation index of at least about 4.0.

126. The method of claim 107, wherein the peptide has a positivity index of at least 150.

127. The method of claim 105, wherein the peptide is present in a dosage range of about 50 μg - 750 μg per kg body weight of peptide per dosage unit.

128. The method as in any one of claims 103-113, wherein the composition further comprises a pharmaceutically acceptable carrier.

129. The method of claim 128, wherein the pharmaceutically acceptable carrier comprises at least one excipient selected from the group consisting of sterile water, sodium phosphate, mannitol, sorbitol, sodium chloride, and any combination thereof.

130. The method as in any one of claims 103-113, wherein the composition is soluble in an aqueous solution at a physiologically acceptable pH.

131. The method as in any one of claims 103-113, wherein said administering comprises a route of administration selected from the group consisting of oral, intravenous, sublingual, transdermal, inhalation, subcutaneous and rectal.

132. The method of claim 131, wherein said administering comprises subcutaneous administration of said composition.

133. The method as in any one of claims 103-113, wherein said composition is administered in non-immunogenic form.

134. The method as in any one of claims 103-113 comprising administering an initial treatment of three to six dosages of said composition over a period of no more than 6 weeks.

135. The method of claim 134 further comprising administering an additional administration of said composition at intervals of between about three months and one year after said initial treatment.

136. The method as in any one of claims 103-113, wherein said initial treatment comprises increasing the dosage with each subsequent additional dosage of said composition.

137. The method as in any one of claims 103-113, wherein said initial treatment comprises decreasing the dosage with each subsequent additional dosage of said composition.

138. The method as in any one of claims 103-113, wherein treatment results in a statistically significant improvement in symptoms caused by the human's immune response to the protein allergen.

139. The method of claim 128, wherein treatment results in at least about 17.5% improvement, as compared to placebo, in symptoms caused by the human's immune response to the protein allergen.

140. The method of claim 128, wherein treatment results in at least about 9% improvement, as compared to placebo, in nasal symptoms caused by the human's immune response to the protein allergen.

141. The method of claim 128, wherein treatment results in at least about 17.5% improvement, as compared to placebo, in lung symptoms caused by the human's immune response to the protein allergen.

142. The method of claim 139, wherein the treatment results in at least about 23% improvement.

143. The method of claim 139, wherein the treatment results in at least about 31% improvement.

144. The method of claim 139, wherein the treatment results in at least about 28.5 % improvement.